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Award Number: W81XWH-09-2-0065

TITLE: Trial of Naltrexone and Dextromethorphan for Gulf War Veterans' Illnesses

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REPORT DATE:
July 2014

TYPE OF REPORT:
Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

☒ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
July 2014	Annual	1 JUL 2013 - 30 JUN 2014

4. TITLE AND SUBTITLE
Trial of Dextromethorphan and Naltrexone for Gulf War Veterens' Illness

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-09-2-0065

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
. East Carolina University
Greenville, NC 27858-4363

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This research study aims to expand the field of knowledge of Gulf War Illness. The research may provide initial proof of the innovative hypothesis that Gulf War Illness is related to low grade neuron-inflammation, which can be down regulated, by Naltrexone and Dextromethorphan. This is untested but potentially ground breaking concept that could provide, both an enhanced understanding of, and beneficial treatment for, Gulf War Illnesses. Research at the National Institute of Environmental Health and other facilities has proven that naltrexone and dextromethorphan reduce inflammation in the brain. Clinical trials in humans with low dose naltrexone have established benefits in syndromes related to Gulf War Illness such as fibromyalgia. We have successfully enrolled 41 subjects in the study, and anticipate obtaining important data by the end of the coming year. A no cost extension has been obtained to complete the study.

15. SUBJECT TERMS- Gulf War Illness, naltrexone, dextromethorphan

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION

Gulf war veterans' illnesses comprise distinct clusters of symptom-defined illnesses (1,2) for which there are neither diagnostic tests nor effective treatments. Gulf war veterans had variable exposures to a number of chemicals (3), including organophosphate insecticides, pyrethrum-related insecticides, DEET, Pyridostimine bromide, smoke from oil well fires, and Sarin gas. Gulf war veterans' illnesses may reflect an inflammatory cycle involving the brain which may be a common mechanism of many neurological conditions, whether initiated by toxic exposures, infection, or trauma. In this theory, central nervous system inflammation initiated by toxic exposures and sometimes exacerbated by subsequent exposures is a component of illness hypothesized to explain the neurological manifestations. Substance P release at sensory nerve endings is an explanation for the peripheral pain manifestations of illness.

This theory suggests that novel anti-inflammatory drugs may be of benefit in symptom-defined illnesses related to a cycle of inflammation. Dr. J. S. Hong's laboratory at the National Institute of Environmental Health Sciences has demonstrated that Morphine-related analogs, including Naltrexone and Dextromethorphan, have great potency in anti-inflammation and neuroprotective effects. Naltrexone is a safe and readily available generic medication. Dextromethorphan is also a safe and readily available generic medication that is available without a prescription as a cough medication. Results from several clinical trials showed that Naltrexone is effective in several inflammation-related diseases, such as neurogenic pain, movement disorders, etc. In addition, there were no obvious side effects in patients taking this drug for six months. This project is a randomized double-blinded study for treating ill Gulf war veterans with Naltrexone and Dextromethorphan. Laboratory tests for markers of inflammation including neurogenic inflammation will be performed pre- and post-treatment, to see if these markers are elevated and if so, to see if treatment modulates these markers.

BODY

The major accomplishment of the past year was having 34 subjects successfully complete the naltrexone protocol, with an additional 3 patients scheduled to complete the protocol. Fourteen subjects successfully completed the dextromethorphan protocol, with another 11 patients scheduled to complete the protocol. Recruitment remains a challenge. We have screened 301 ill Gulf War Veterans who have responded to advertisements, but the rejection rate has been high. Reasons for not participating were not meeting the exclusion criteria, particularly those on multiple medications with potential drug interactions with study drugs, or not meeting inclusion criteria, particularly those not meeting the case definition. The rate of veterans meeting inclusion or exclusion criteria but rejecting enrollment was low. After having about 100% completion of enrollees the first two years, we have encountered drop out. Nonetheless, as we enter the last year of the study, our initial power analysis based on the use of study drugs for syndromes overlapping with Gulf War Illness indicates that we should have sufficient power to detect differences between study drugs and placebo

KEY RESEARCH ACCOMPLISHMENTS

The most significant accomplishment during the past year was successfully recruiting and enrolling a number of veterans with Gulf War Illness in the clinical trials. Data collection has been complete with no gaps on last data review. The level of adverse reactions to study drugs has been minimal.

Screening interview	301
Consent obtained	50
Completed naltrexone protocol	34
Completed dextromethorphan protocol	14
Withdrew	3
Loss to follow-up	8
Currently enrolled in naltrexone protocol	3
Currently enrolled in dextromethorphan protocol	11
Discontinued naltrexone due to adverse reaction (subjective dizziness)	1
Discontinued dextromethorphan due to adverse reaction	0

We have performed nerve growth factor analyses using an ELIZA assay on samples from those participants who have completed courses of either naltrexone versus placebo or naltrexone versus placebo. The samples have not been unblended, but time point variability has been observed. We are preparing to perform the LIncoplex assay for neuroinflammation cytokines on these samples.

REPORTABLE OUTCOMES

We have not yet unblinded the participants who have completed the study. Data analysis will take place when the last completion of study protocol is accomplished, which will be in the first half of 2015. No data has been analyzed. There has been only one adverse event, with one subject reporting subjective dizziness while taking naltrexone. This was discontinued and he proceeded to the dextromethorphan protocol. One individual reported loose stools while on one of the dextromethorphan arms, which resolved after he completed the course. He did not inform us of this reaction until after he came for his end of course evaluation and did not stop taking the course of study drug versus placebo.

CONCLUSIONS

We anticipate finishing the study over the next Successful recruitment, enrollment, compliance, and data collection has been gratifying. We anticipate a successful outcome to the study aims and objectives.

REFERENCES

1. Haley RW, Hom J. Is there a Gulf War Syndrome? Searching for syndromes by factor analysis of symptoms. JAMA. 1997;277:215-22. Erratum in: JAMA 1997 Aug 6;278(5):388.
2. Haley RW, Hom J, Roland PS, Bryan WW, Van Ness PC, Bonte FJ, Devous MD Sr, Mathews D, Fleckenstein JL, Wians FH Jr, Wolfe GI, Kurt TL. Evaluation of neurologic function in Gulf War veterans. A blinded case-control study. JAMA. 1997;277:223-30.
3. Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the Gulf War. A cross-sectional epidemiologic study. JAMA. 1997:15;277:231-7.